IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CHIESI USA, INC., CORNERSTONE BIOPHARMA, INC., and EKR THERAPEUTICS, LLC, Plaintiffs v. EXELA PHARMA SCIENCES, LLC, EXELA PHARMSCI, INC., and EXELA HOLDINGS, INC., Defendants.	C.A. No. 1:13-cv-01275-GMS

EXPERT DECLARATION OF PROFESSOR ALEXANDER M. KLIBANOV
IN SUPPORT OF PLAINTIFFS' OPENING CLAIM CONSTRUCTION BRIEF

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I, Alexander M. Klibanov, declare as follows:

1. I have personal knowledge of the following matters and, if called to testify, can and will testify thereto.

I. BACKGROUND AND QUALIFICATIONS

2. I am a Professor of Chemistry and Bioengineering at the Massachusetts Institute of Technology ("M.I.T."), where I have been teaching and conducting research for over 35 years and currently hold the Novartis Endowed Chair Professorship (which I also held from 2007 to 2012). In 2012-2013, I was the Roger and Georges Firmenich Endowed Chair Professor of Chemistry and Bioengineering at M.I.T. Up to 2007, I was a Professor of Chemistry and a Professor of Bioengineering at M.I.T., positions I held from 1988 and 2000, respectively. From 1979 to 1988, following my immigration to the United States, I was an Assistant Professor, then an Associate Professor, and thereafter a Full Professor of Applied Biochemistry in the Department of Applied Biological Sciences (formerly the Department of Nutrition and Food Science) at M.I.T.

3. I obtained my M.S. in Chemistry from Moscow University in Russia in 1971 and Ph.D. in Chemical Enzymology from the same University in 1974. Thereafter, I was a Research Chemist at Moscow University's Department of Chemistry for three years. From 1977 to 1979, I was a Post-Doctoral Associate at the Department of Chemistry, University of California in San Diego.

4. Over the last 45+ years as a practicing chemist, I have extensively researched, published, taught, and lectured in many areas of biological, medicinal, bioorganic, and formulation chemistry.

5. I have earned numerous prestigious professional awards and honors. For example, I was elected to the U.S. National Academy of Sciences (considered among the highest honors

that can be given to an American scientist) and also to the U.S. National Academy of Engineering (considered among the highest honors that can be given to an American engineer or applied scientist). I am also a Founding Fellow of the American Institute for Medical and Biological Engineering and a Corresponding Fellow of the Royal Society of Edinburgh (Scotland's National Academy of Science and Letters). In addition, I have received the Arthur C. Cope Scholar Award, the Marvin J. Johnson Award, the Ipatieff Prize, and the Leo Friend Award, all from the American Chemical Society, as well as the International Enzyme Engineering Prize.

6. I currently serve on the Editorial Boards of 12 scientific journals, including "Open Journal of Pharmacology", "Applied Biochemistry and Biotechnology", "Nanocarriers", "Open Access Academic Books in Chemistry", "Biotechnology and Bioengineering", "Journal of Biological Chemistry and Molecular Pharmacology", and "Recent Patents in Biotechnology."

7. I have published some 310 scientific papers in various areas of chemistry and am also a named inventor of 18 issued United States patents and of a number of foreign patents. I have given 370 invited lectures at professional conferences, universities, and corporations all over the world, many dealing with formulation, delivery, and biological evaluation of pharmaceutically active compounds.

8. In addition to my research and teaching activities at M.I.T., I have consulted widely for pharmaceutical, medical device, chemical, and biotechnology companies. They have included both innovator and generic pharmaceutical companies.

9. I have also founded six pharmaceutical companies and have been on the scientific advisory boards and/or boards of directors of those companies and of many others. A number of these consulting, advisory, and directorship activities have dealt specifically with the formulation

of pharmaceutically active compounds. Of particular relevance to this case is my substantial experience with ready-to-use injectable and other parenteral formulations of numerous pharmaceutical compounds (including intravenous infusions, subcutaneous injections, and intramuscular injections), as well as with antihypertensive drugs. My Curriculum vitae, attached hereto, summarizes my education and academic professional experience. Included in it is a list of my publications and issued U.S. patents.

10. In the last 4+ years, I have provided expert testimony in the following matters (in all cases, on behalf of the party listed first): *Boehringer Ingelheim v. Barr*, U.S.D.C. for the District of Delaware; *Apotex v. Unigene et al.*, U.S.D.C. for the Southern District of New York; *Warner-Lambert v. Teva et al.*, U.S.D.C. for the District of New Jersey; *Novartis v. Mylan et al.*, U.S.D.C. for the District of New Jersey; *Genzyme v. Sandoz*, U.S.D.C. for the District of Delaware; *Lupin v. Paddock et al.*, U.S.D.C. for the Southern District of New York; *Teva* and *Roxane v. Hoffmann-LaRoche*, U.S.D.C. for the District of New Jersey; *Genzyme v. Impax et al.*, U.S.D.C. for the District of Maryland; *LEO Pharma v. Tolmar*, U.S.D.C. for the District of Delaware; *Butamax v. Gevo*, U.S.D.C. for the District of Delaware; *The Medicines Company v. Mylan et al.*, U.S.D.C. for the Northern District of Illinois; *The Medicines Company v. Hospira et al.*, U.S.D.C. for the District of Delaware; *Novartis v. Watson et al.*, U.S.D.C. for the District of Delaware; *UCB v. Mallinckrodt*, U.S.D.C. for the District of Delaware; *Shire v. Amneal et al.*, U.S.D.C. for the District of New Jersey; *Dr. Reddy's Laboratories v. Fresenius Kabi*, U.S.D.C. for the District of Delaware; *Galderma v. Actavis*, U.S.D.C. for the Northern District of Texas; *Chiesi USA v. Sandoz Inc. et al.*, U.S.D.C. for the District of New Jersey.

II. ANTICIPATED TESTIMONY AND MATERIALS CONSIDERED

11. I have been informed by their counsel ("Counsel") that the plaintiffs Chiesi USA, Inc. (formerly Cornerstone Therapeutics Inc.), Cornerstone BioPharma, Inc., and EKR

Therapeutics, LLC (collectively "Chiesi") have sued defendants Exela Pharma Sciences, LLC, Exela PharmSci, Inc., and Exela Holdings, Inc. (collectively, "Exela" or "Defendants") for infringement of U.S. Patent Nos. 7,612,102 ("the '102 patent"), 7,695,290 ("the '290 patent"), 7,659,291 ("the '291 patent"), and 8,455,524 ("the '524 patent") (collectively, "the patents in suit"), all of which have nearly the same specification.

12. In connection with the claim construction activities in this action, I have been asked by Counsel to comment on the meaning of certain claim terms of the patents in suit, which were identified by the parties for claim construction. Counsel has explained that there are two types of evidence to guide claim construction: intrinsic and extrinsic (e.g., technical dictionaries, learned treatises, and expert testimony for the latter). I have been advised to look first and foremost to the intrinsic evidence of record, i.e., the patent claims, specification, and prosecution history.

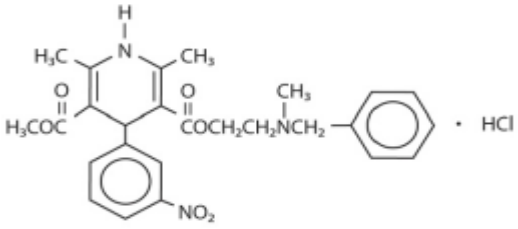
13. In connection with this declaration, I have reviewed the materials listed in Appendix B. Unless otherwise stated, the exhibits referenced herein are those (i) referenced in the Joint Appendix of Intrinsic Evidence ("JA Ex. __") or (ii) attached to the Declaration of Angus Chen, Esq., in Support of Plaintiffs' Opening Claim Construction Brief ("Ex. __").

14. The opinions presented below are based on my education, knowledge, and experience acquired in over 45+ years of practicing and consulting in the fields of medicinal, bioorganic, and formulation chemistry, as well as the relevant information available to me as of the date of this declaration.

III. BACKGROUND

15. The product at issue in this case is Cardene® I.V. Premixed Injection. This product is supplied as a single-use, ready-to-use, iso-osmotic solution for intravenous ("I.V.")

administration. The active pharmaceutical ingredient ("API") in Cardene® I.V. Premixed Injection is nicardipine hydrochloride, whose chemical structure is as follows:



IV. A PERSON OF ORDINARY SKILL IN THE ART

16. I understand that terms in patent claims must be interpreted as they would have been understood by a hypothetical person of ordinary skill in the art to which the invention related as of the date of the invention ("POSA"), who is presumed to be aware of all pertinent prior art. I have been asked by Counsel to use April 18, 2007, as the relevant date.

17. To assess the education and expertise of a POSA for the patents in suit, Counsel has instructed me to consider the following factors: the educational level of the inventors; the type of problems encountered in the art and the prior-art solutions to those problems; the rapidity with which innovations are made; the sophistication of the technology; and the educational level of workers in the field. I understand that not all factors may be present in every case and that one or more of them may predominate.

18. I understand that one of the inventors of the patents in suit had a Bachelor of Science degree and a few years of work experience in the pharmaceutical sciences.

19. It is my opinion that a POSA for the patents in suit would have at least a Bachelor of Science degree in Pharmaceutical Sciences or a related field, such as Chemistry, Pharmacy, Biology, or Chemical Engineering, plus a few years of practical experience in pharmaceutical sciences or a related field (or a similar education and experience). I reserve the right to

supplement my opinions herein if Exela provides a definition of a POSA at a later date that differs from mine.

V. SUMMARY OF PROPOSED CLAIM CONSTRUCTIONS

20. The following table identifies the claim terms that I have been asked to opine on and the construction for each as I believe it would be understood by a POSA.

Claim Term	Patents / Claims	Construction	Section in Declaration
"a pre-mixed aqueous solution"	'102 patent[1], claims 1, 5–7, 8–11 '290 patent[2], claims 1, 7, 11 '291 patent[3], claims 3, 7, 8, 12 '524 patent[4], claims 1–3, 7, 8, 12, 19–22, 27, 28	"a ready-to-use pharmaceutical composition that is an aqueous solution already mixed from the point of manufacture and is stable, allows medical personnel to use prepared containers containing an injectable formulation off the shelf without additional preparation, avoids potential contamination problems, and eliminates dosage errors"	VI.A
"one year [*or* three months] at room temperature"	'102 patent, claims 1, 5, 6, 8–11 '290 patent, claims 1, 7, 11 '291 patent, claims 1–3, 8 '524 patent, claims 1–3, 8, 19–22	one year or three months "full-term at room temperature"	VI.B
"buffer"	'102 patent, claims 1, 5–7, 12–15 '290 patent, claims 1, 5 '291 patent, claims 1, 2 '524 patent, claims 1–3, 8	"a system capable of maintaining the pH within an optimal pH range"	VI.C

[1] Claims 8–11 of the '102 patent recite "the aqueous solution."

[2] Claim 1 of the '290 patent recites "the pre-mixed composition."

[3] Claims 7 and 12 of the '291 patent recite "the pre-mixed aqueous solution."

[4] Claims 19–22 of the '524 patent recite "the aqueous solution." Claims 7, 12, 27, and 28 recite "the pre-mixed aqueous solution."

Claim Term	Patents / Claims	Construction	Section in Declaration
"buffer in an amount to maintain pH from about 3.6 to about 4.7"	'102 patent, claims 1, 5-7	"a system capable of maintaining the pH within an optimal pH range in an amount to maintain pH from about 3.6 to about 4.7"	VI.C

VI. PROPOSED CLAIM CONSTRUCTIONS

A. "a pre-mixed aqueous solution"

21. The following table compares Chiesi's proposed construction with Defendants' proposed constructions for the claim term "a pre-mixed aqueous solution":

Claim Term	Chiesi's Proposed Construction	Defendants' Proposed Constructions
"a pre-mixed aqueous solution"	"a ready-to-use pharmaceutical composition that is an aqueous solution already mixed from the point of manufacture and is stable, allows medical personnel to use prepared containers containing an injectable formulation off the shelf without additional preparation, avoids potential contamination problems, and eliminates dosage errors"	an aqueous solution that does not require reconstitution or dilution before administration to a patient

22. In my opinion, a POSA reading the claims in view of the specifications and with the prosecution histories of the patents in suit in mind would define "a pre-mixed aqueous solution" consistent with its plain and ordinary meaning as proposed by Chiesi in the table above.

23. Chiesi's proposed construction stems from the specification of the patents in suit:

Chiesi's Proposed Construction	**Corresponding Portions of the Patent Specification**
a ready-to-use pharmaceutical composition that is an aqueous solution already mixed from the point of manufacture and is stable, allows medical personnel to use prepared containers containing an injectable formulation off the shelf without additional preparation, avoids potential contamination problems, and eliminates dosage errors	the term "pre-mixed", as used herein, means a ***pharmaceutical composition that is already mixed from the point of manufacture*** and does not require dilution or further processing before administration. * * * the ***ready-to-use***, ***injectable formulations*** described herein are ***stable, allow medical person[ne]l to use prepared containers containing an injectable formulation off the shelf without additional preparation, avoid potential contamination problems, and eliminate dosage errors***. (*See, e.g.*, JA Ex. A, '102 patent, col.11, ll.25-29, and col.1, ll.52-57; emphasis added.)

The words highlighted in the portions of the specification copied in the table above are the same as those used in Chiesi's proposed construction.

24. A POSA would understand that the inventions claimed in the patents in suit are ready-to-use, pre-mixed pharmaceutical compositions that "require no dilution prior to administration." (JA Ex. A, '102 patent, col.2, ll.20-21.) (S)he would not understand "a pre-mixed aqueous solution" to include a concentrated injectable solution that requires additional preparation, mixing, or dilution steps before administration to a patient. The patent specification explicitly contrasts the pharmaceutical compositions that are pre-mixed from the point of manufacture from those that are not (*e.g.*, an ampule of a concentrated solution that requires dilution and mixing after the point of manufacture, namely at the point of care):

> The premixed pharmaceutical compositions described herein comprise nicardipine or a pharmaceutically acceptable salt thereof as the active ingredient, at least one tonicity agent and a buffer. As used herein, the term "***pre-mixed***" refers to a pharmaceutical

> composition that ***does not require reconstitution or dilution*** before administration to a patient. ***In contrast*** to ***ampul formulations*** comprising nicardipine hydrochloride ***that must be diluted prior to use in a diluent and container selected by hospital personnel***, the premixed pharmaceutical compositions provided herein are stable at room temperature for 6 months or longer due to the inclusion of a buffer capable of maintaining the pH within an optimal pH range, which is typically between 3.6 to about 4.7.

(*See, e.g.*, JA Ex. A, '102 patent, col.3, ll.7-19; emphasis added.) Hence a POSA would understand that a "pre-mixed" formulation in the context of the patents in suit differs from a point of care formulation that requires dilution/mixing by hospital staff prior to administration.

25. A POSA also would understand the disadvantages of a concentrated injectable formulation that was not ready-to-use from the point of manufacture, but instead required dilution at the point of care. The specification expressly describes the advantages of the pre-mixed formulations described in the asserted claims of the patent in suit as compared to formulations that are not pre-mixed:

> Additional benefits of the pre-mixed, ready-to-use, injectable pharmaceutical compositions include convenience and ease of use ***as compared to an ampul formulation***, improved safety for patients due to elimination of dosage errors and solution contamination, reduction of medical waste, and ease of administration in emergency situations.

(*See, e.g.*, JA Ex. A, '102 patent, col.2, ll.4-9; emphasis added.)

26. A POSA also would understand that the claimed pre-mixed aqueous solutions are manufactured by the drug-product manufacturer and dispensed into a container for storage and direct administration to patients. My opinion in this regard is supported by the specification which describes methods for making the pre-mixed aqueous solutions of the patents in suit:

> Methods for making a ***premixed*** nicardipine hydrochloride formulation suitable for intravenous administration comprise the steps of providing an effective amount of nicardipine hydrochloride in a solution comprising one or more tonicity agents, a buffer, and optionally, one or more cosolvents. Sufficient water

> is added to make up the final volume. If required, the pH of the solution can be adjusted using a suitable pH adjuster. The compositions are dispensed in pharmaceutically acceptable containers for ***storage and direct administration to patients***.

(*See, e.g.*, JA Ex. A, '102 patent, col.2, ll.28-37; emphasis added.)

27. Because the pre-mixed aqueous solution is dispensed by the drug-product manufacturer into a container that will be used for storage and direct administration to patients as described above, a POSA would also understand that the compositions must be stable from the point of manufacture. My opinion in this regard is supported by disclosures in the patent specification that summarize the pharmaceutical compositions of the invention:

> By providing ready-to-use, premixed pharmaceutical compositions with a buffered pH, these pharmaceutical compositions are ***stable*** at room temperature for at least one year.

and also by disclosures for making the claimed compositions:

> The order in which various components comprising the compositions is added to the buffered solution is not critical, provided that the resulting compositions are ***stable*** and are suitable for continuous intravenous infusion.

(*See, e.g.*, JA Ex. A, '102 patent, col.1, ll.64-67, and col.8, ll.33-36, respectively; emphasis added.)

28. The intrinsic record, including the specification as described above in ¶¶ 24 and 25, provides clear and unequivocal indications that the patentees intended the claims to exclude (and, in fact, expressly disclaimed) point-of-care embodiments.

29. The U.S. provisional application to which each of the patents in suit claims priority also supports my opinion, providing additional express indications by the patentees that the claimed compositions do not include point-of-care embodiments. (JA Ex. E, U.S. App. No. 60/793,074 ("'074 Application").) The '074 Application indicates that the pharmaceutical compositions of the patents in suit provide a formulation that is "ready-to-use" because it "***do[es]***

not require dilution or further processing before administration," "is stable," and is for "immediate use":

- "'pre-mixed', as used herein, means a pharmaceutical composition that is already mixed from the point of manufacture and ***does not require dilution*** or further processing before administration;"
- "It would be beneficial to develop a pre-mixed, ***ready-to-use***, injectable cardiac formulation that is ***stable*** and could be pulled off the shelf for ***immediate use***;"
- "a pre-mixed, ***ready-to-use***, injectable formulation would be more convenient and easier to use than an ampul formulation, [and] it would be ***safer*** for both patients and hospital staff;"
- "It would also be beneficial to develop the above [pre-mixed, ***ready-to-use***, injectable] formulation such that it is ***stable*** at room temperature for long periods of time . . . and could be stored in a clinical setting for months, or even years to ensure that this form of treatment was readily available;" and
- "the compositions are more convenient and easier to use than ampul formulations because they ***do not require dilution*** before infusion; they are ***ready to use***."

(JA Ex. E, '074 Application at A-95–97; emphasis added.)

30. The '074 Application also indicates that the claimed pre-mixed pharmaceutical compositions are safer than point of care injectable products because their "correct concentration and sterility are assured," as is "safe[ty] for hospital staff":

- "Because the compositions do not require dilution before infusion, they are ***safer*** for patients because they reduce or eliminate microbiological contamination that may occur during dilution;"
- "Patient ***safety*** is also enhanced because the compositions reduce or eliminate potential medication errors due to mathematical errors that may occur during dilution;" and
- "the compositions are ***safer*** for hospital staff because they eliminate the hazards, such as glass cuts, associated with glass ampuls."

(JA Ex. E, '074 Application at A-97; emphasis added.)

31. The prosecution histories of the patents in suit also support my opinions. During prosecution, the applicants indicated that their invention provided a "***storage stable, ready-to-use***

nicardipine hydrochloride intravenous product." (JA Ex. G, July 6, 2009 Amendment, A-143; *see also* JA Ex. H, Brittain Declaration, A-153 (emphasis added).) The applicants also expressly contrasted the claimed pre-mixed aqueous solutions with point of care injectable drug products that are not pre-mixed and require dilution:

- "The requirement of dilution can result in a lag time that prevents a patient in an acute setting from receiving the drug in a timely fashion;"
- "The breaking of the ampul neck may result in exposing the patient to glass contamination of the product;"
- "There is an increased probability of dosing errors [when] requiring health care professionals to dilute the product;"
- "The diluted form must be discarded in 24 hours due to stability issues;" and
- "The selection of an inappropriate diluent can have an adverse effect on the stability . . ."

(JA Ex. G, July 6, 2009, Amendment, A-142–143; *see also* Ex. H, Brittain Declaration, A-153.) Thus, a POSA in the relevant timeframe would recognize that the pre-mixed aqueous solutions of the patents in suit are a safer, ready-to-use, manufacturer-prepared I.V. drug product compared to an injection product that requires additional mixing at, or just prior to, the point of care before administration to a patient.

32. Notably, during the prosecution of the '102 patent, the inventors presented the Examiner at an interview with physical samples of both the claimed pre-mixed ready-to-use nicardipine composition and the concentrated point-of-care nicardipine product. (JA Ex. F, June 16, 2009, Examiner Interview Summary Record, A-134.) The Examiner summarized the interview and stated (*id.*; emphasis added):

> Applicant described [that] the ***prior art teachings*** are directed toward the ***concentrated*** form of nicardipine, which ***is not the same as the premixed formulation*** presented in the claims. The stability of ***the premixed formulation*** was discussed as an improvement over previous ***diluted samples of the prior art concentrate***.

Thus, a POSA would understand that the claimed pre-mixed aqueous solutions of the patents in suit do not include point-of-care dosage forms, including concentrated or lyophilized nicardipine products and diluted/reconstituted forms thereof.

33. As indicated in the ¶ 21 table above, Defendants propose to construe the "a pre-mixed aqueous solution" claim term as "an aqueous solution that does not require reconstitution or dilution before administration to a patient." (ECF No. 48, Ex. A at 1.) I find the construction proposed by Defendants ambiguous, too broad, and not in line with how a POSA would understand the claim term when read in view of the specifications and with the prosecution histories of the patents in suit in mind. A POSA would not understand "a pre-mixed aqueous solution" in the context of the claims to encompass diluted point-of-care dosage forms as Defendants' construction allows.

34. As described above, a POSA would understand that, in the context of the patents in suit, a manufacturer-prepared, ready-to-use nicardipine I.V. solution with an FDA-approved label used by medical personnel off the shelf without additional preparation was indeed "pre-mixed." In contrast, (s)he would understand that a nicardipine I.V. solution prepared (*i.e.*, mixed and/or diluted) in a hospital pharmacy or otherwise was ***not*** "pre-mixed" because such solution required mixing ***after*** the point of manufacture and at the point of care.

35. My opinion that a POSA would understand that the claimed "pre-mixed aqueous solution" is prepared already mixed and ready-to-use from the point of drug-product manufacture is also supported by a Special Report in the journal *Hospital Pharmacy*. (Ex. 1, David W. Bates *et al.*, *Consensus Development Conference Statement on the Safety of Intravenous Drug Delivery Systems: Balancing Safety and Cost*, Vol. 35, No. 2, pp.150-155 ("Bates").) This report explains that "Manufacturer-Prepared Products (eg, ***Premixed*** or Frozen)" are prepared ready-to-use by a

drug-product manufacturer, thus are readily available, and do not require dose calculation by hospital staff . (Ex. 1, Bates at 151-152 (emphasis added).) Chiesi's proposed construction is consistent with Bates' description of manufacturer-prepared pre-mixed injectable solution products and properly excludes dosage forms that are mixed after the point of manufacture (*i.e.*, diluted point-of-care dosage forms) as Defendants' broad construction allows.

36. Additionally, Defendants' proposed construction is redundant with other claim limitations expressly recited in certain claims of the patents in suit that also recite the "pre-mixed aqueous solution" claim term. For example, after inserting Defendants' proposed construction for the "pre-mixed aqueous solution" claim term (in brackets below), claim 1 of the '524 patent will read as follows (emphasis added):

> 1. A method for treating acute elevations of blood pressure in a human subject in need thereof, said method comprising parenterally administering [an aqueous solution that ***does not require*** reconstitution or ***dilution before administration*** to a patient] comprising from about 0.1 to 0.4 mg/mL nicardipine or a pharmaceutically acceptable salt thereof; a tonicity agent; and a buffer; wherein the aqueous solution ***requires no dilution before administration*** and has a pH from about 3.6 to about 4.7, the aqueous solution stored in a container such that the aqueous solution is in contact with non-polar polymers, the aqueous solution when stored in the container for at least three months at room temperature exhibiting (i) less than a 10% decrease in the concentration of nicardipine hydrochloride and (ii) a total impurity formation of less than about 3%.

This unnecessary redundancy further supports my opinion that a POSA reading the claims in view of the specifications of the patents in suit would define "a pre-mixed aqueous solution" consistent with its plain and ordinary meaning, as proposed by Chiesi in the table in ¶ 21 above, and not as Defendants propose.

B. "one year [*or* three months] at room temperature"

37. The following table compares Chiesi's proposed constructions for the "one year at room temperature" and "three months at room temperature" claim terms with Defendants':

Claim Term	Chiesi's Proposed Construction	Defendants' Proposed Construction
"one year [*or* three months] at room temperature"	"one year [*or* three months] full-term at room temperature"	No construction necessary

38. These "at room temperature" claim limitations refer to conditions, namely time and temperature, under which the claimed compositions exhibit (i) a less than 10% decrease in the concentration of nicardipine hydrochloride (*i.e.*, in the drug potency) and (ii) a total impurity formation of less than about 3%. (*See, e.g.*, JA Ex. A, '102 patent, claim 1; Ex. C, '291 patent, claim 1.)

39. Chiesi's proposed constructions are supported by the language of the claims themselves. For example, claim 1 of the '102 patent recites (emphasis added):

> 1. A pharmaceutical composition for parenteral administration comprising a pre-mixed aqueous solution with a pH from about 3.6 to about 4.7 comprising:
>
> from about 0.1 to 0.4 mg/mL nicardipine hydrochloride;
>
> a tonicity agent selected from (i) about 4.5% to about 5% dextrose or (ii) about 0.8% to about 0.9% sodium chloride;
>
> and a buffer in an amount to maintain pH from about 3.6 to about 4.7;
>
> the aqueous solution contained in a pharmaceutically acceptable container such that the solution does not come into contact with polar polymers;
>
> the aqueous solution when stored in the container for ***at least*** one year at room temperature exhibiting (i) less than a 10% decrease in the concentration of nicardipine hydrochloride and (ii) a total impurity formation of less than about 3%.

Because "one year at room temperature" is preceded by the phrase "at least," a POSA would understand this term to mean one full year or longer at room temperature.

40. Similarly, claim 1 of the '291 patent recites (emphasis added):

> 1. A method for treating acute elevations of blood pressure in a human subject in need thereof, said method comprising
>
> parenterally administering a composition comprising from about 0.1 to 0.4 mg/mL nicardipine or a pharmaceutically acceptable salt thereof;
>
> a tonicity agent;
>
> and a buffer;
>
> wherein the composition requires no dilution before administration and has a pH from about 3.6 to about 4.7, the composition when stored in container for ***at least*** three months at room temperature exhibiting (i) less than a 10% decrease in the concentration of nicardipine or pharmaceutically acceptable salt thereof and (ii) a total impurity formation of less than about 3%.

Because "three months at room temperature" is preceded by the phrase "at least," a POSA would understand this term to mean three full months or longer at room temperature.

41. My opinions in this regard are further supported by the patent specification:

> Described herein are ready-to-use, premixed pharmaceutical compositions of nicardipine or pharmaceutically acceptable salts thereof, which are suitable for continuous intravenous infusion. By providing ready-to-use, premixed pharmaceutical compositions with a buffered pH, these pharmaceutical compositions are ***stable at room temperature for at least one year***. When stored at room temperature, the pharmaceutical compositions exhibit between 0% to about 15% loss of drug and between 0% to about 3% (w/w) total impurity formation ***over an eighteen to twenty four month period***.

and also:

> The ready-to-use pharmaceutical compositions described herein exhibit 0% to 15% drop in drug concentration and 0% to 3% formation of impurities when maintained at room temperature for 6 to at least 24 months. Typically, the pharmaceutical compositions are ***stable when maintained at room temperature for at least 6***

months, at least 12 months, at least 18 months, and at least 24 months.

(*See, e.g.*, JA Ex. A, '102 patent, col.1, l.61-col.2, l.3, and col.3, ll.43-48, respectively; emphasis added.)

42. A POSA would understand the plain and ordinary meaning of these "at room temperature" claims terms—in the context of the entire clauses within which each appears, as well as the specifications and prosecution histories of the patents in suit—to be one year or three months "full-term at room temperature." As described above in ¶¶ 39–41, a POSA would understand that the time period recited in these claim terms means the full-term of the time period stated (*e.g.*, one year means twelve months).

43. Similarly, a POSA would understand that the temperature recited in these claim terms means the stated temperature (*i.e.*, room temperature or 25°C). This view is supported by the examples of the patents in suit. For instance, in Example 2, the inventors explicitly discuss the assumptions used when making long-term room temperature stability extrapolations (*i.e.*, a hypothesis) in the patents in suit. (*See, e.g.*, JA Ex. A, col.15, ll.1-9.) The inventors also expressly cite a reference by K.A. Connors *et al.*, entitled *Chemical Stability of Pharmaceuticals*, which indicates that such stability hypotheses "should be confirmed with ***full-term***, ***normal studies***." (JA Ex. I, *Chemical Stability of Pharmaceuticals*, A-174 (emphasis added).) Thus, a POSA would understand that a long-term room-temperature stability hypothesis needs to be ***verified*** under "***full-term, normal***" (*i.e.*, real-time) conditions ***at room temperature***.

C. "buffer" / "buffer in an amount to maintain pH from about 3.6 to about 4.7"

44. The following table compares Chiesi's proposed construction with Defendants' proposed constructions for the claim terms "buffer" and "buffer in an amount to maintain pH from about 3.6 to about 4.7":

Claim Term	Chiesi's Proposed Construction	Defendants' Proposed Constructions
"buffer"	"a system capable of maintaining the pH within an optimal pH range"	"component of the composition (or aqueous solution) separate and distinct from nicardipine hydrochloride, tonicity agent, cosolvent, water and/or pH adjuster that has sufficient buffering capacity to maintain an optimal pH range throughout the shelf-life of the product."
"buffer in an amount to maintain pH from about 3.6 to about 4.7"	"a system capable of maintaining the pH within an optimal pH range in an amount to maintain pH from about 3.6 to about 4.7"	"component of the composition (or aqueous solution) separate and distinct from nicardipine hydrochloride, tonicity agent, cosolvent, water and/or pH adjuster that has sufficient buffering capacity to maintain a pH range from about 3.6 to about 4.7 throughout the shelf-life of the product."

45. In my opinion, a POSA reading the claims in view of the specifications and prosecution histories of the patents in suit would understand the claim terms "buffer" and "buffer in an amount to maintain pH from about 3.6 to about 4.7" consistent with their plain and ordinary meaning as proposed by Chiesi in the table above. Note that Chiesi's proposed construction for the term "buffer" is repeated in its proposed construction for the term "buffer in an amount to maintain pH from about 3.6 to about 4.7." Thus, my opinions below concerning the "buffer" claim term apply equally to the claim term "buffer in an amount to maintain pH from about 3.6 to about 4.7."

46. Chiesi's proposed construction of the claim term "buffer" as "a system capable of maintaining the pH within an optimal pH range" is consistent with how the patents in suit define this term. (*See, e.g.*, JA Ex. A, '102 patent, col.3, ll.15-19.) A POSA would understand that Chiesi's proposed construction encompasses embodiments where the buffer is a system, comprising either a single or multiple agents, that helps maintain the pH within an optimal range.

(*Ibid.*, col.9, ll.18-19, and col.13, ll.28-30.) This view is also supported by the '074 Application, which indicates that the pharmaceutical compositions of the patents in suit "may comprise multiple buffering agents." (JA Ex. E, '074 Application at A-101.) (S)he would not understand the claim term "buffer" in the context of the patents in suit as Defendants propose, which includes additional limitations that are contradicted by the patent specifications and the intrinsic record.

47. A POSA would understand that in aqueous (*i.e.*, water based) solutions, pH is a measure of acidity and/or alkalinity. (Ex. 4, *Merriam-Webster Medical Desk Dictionary* (1996) at 608.) S(he) would also understand that pH is defined as the negative logarithm of effective hydrogen-ion concentration (or, more precisely, of hydrogen ion activity), *i.e.*, $pH = -\text{Log}[H^+]$, and that at room temperature (in that case 22°C) a pH of 7.0 represents a neutral solution, pH values above 7.0 represent basic solutions, and pH values below 7.0 represent acidic solutions. Furthermore, the higher the pH the more basic (alkaline) the aqueous solution is, and the lower the pH the more acidic the aqueous solution is. (*Ibid.*)

48. A POSA would understand that the pH of a drug solution affects the degree of ionization (*i.e.*, net charge) of the drug molecule in solution, which, in turn, affects the solubility and reactivity of the drug. For a drug solution packaged in a pharmaceutically acceptable container, the pH of the drug solution impacts to what extent the drug adsorbs into the container's inner surfaces and/or degrades to form impurities. Thus, a POSA would understand that maintaining the acidity/alkalinity of an aqueous solution—measured through its pH—provides a drug solution in a range that ensures adequate solubility and remaining potency, and also minimizes degradation and impurity formation.

49. The patents in suit describe how pH impacts nicardipine hydrochloride solubility, remaining concentration in solution (*i.e.*, remaining potency), and stability (*e.g.*, impurity formation). (*See, e.g.*, JA Ex. A, '102 patent, col.13, ll.33-35; col.15, ll.10-22; *see also* JA Ex. E, '074 Application at A-101.) Specifically, they describe "a buffer capable of maintaining the pH within an optimal pH range" as one way to solve these issues. (JA Ex. A, '102 patent, col.3, ll.7-18.)

50. The patents in suit also state that "as the pH of the pharmaceutical composition increases, the aqueous solubility of nicardipine decreases. As a result, it is difficult to solubilize nicardipine close to physiological pH." (JA Ex. A, '102 patent, col.13 ll.35-38; *see also* JA Ex. E, '074 Application at A-101.) Thus, a POSA would understand that lowering pH, and thus increasing the ionization (protonation) of nicardipine, improves nicardipine's solubility.

51. The patents in suit also describe how pH impacts potency and impurity formation in nicardipine hydrochloride solutions. Example 2 discloses that "loss in product potency (drop in % drug remaining) due to degradation and adsorption on to the bag surface increased as the formulation pH was increased." (JA Ex. A, '102 patent, col.15, ll.10–13.) Example 2 also discloses that "as the pH was decreased, the total impurities increased." (*Ibid.*, col.15, ll.21–22.) A POSA would understand that these results demonstrate the importance of maintaining pH within a certain range to ensure that nicardipine remains soluble, its potency is maintained, and its impurity formation is minimized. The patents in suit describe using "a buffer capable of maintaining the pH within an optimal pH range" to accomplish such outcome. (*Ibid*., col.3 ll.17-18.) The specification also describes that "the compositions may comprise ***multiple*** buffering agents," not just a single agent.[5] (*Ibid*., col.13, ll.29-30 (emphasis added); *see also* JA Ex. E,

[5] As used herein "agent" is used interchangeably with "component" and "substance".

’074 Application at A-101.) Indeed, the specification expressly contemplates the use of a multi-agent “buffer system” to maintain a desired pH. (JA Ex. A, ’102 patent, col.9 ll.18-19.)

52. As indicated above in ¶ 44, Defendants propose to construe “buffer” as “[c]omponent of the composition (or aqueous solution) ***separate and distinct from*** nicardipine hydrochloride, tonicity agent, cosolvent, water and/or pH adjuster that has sufficient buffering capacity to maintain an optimal pH range ***throughout the shelf-life of the product***.” (emphasis added.) In my opinion, as described below, this construction is not consistent with both the patents in suit and the scientifically accepted understanding of the term “buffer”. In particular, Defendants’ proposed construction (i) adds limitations that are not present in the patent specification, and (ii) imports limitations based on narrow examples that are not representative of the overall teachings in the specification.

53. The patents in suit provide no basis for construing “buffer” as “***separate and distinct from*** nicardipine hydrochloride, tonicity agent, cosolvent, water and/or pH adjuster” as Defendants propose. I see no disclosure in the patent specification that requires a buffer to be separate and distinct from other formulation components. Defendants’ proposed construction means that a buffer cannot be, for example, the pH adjuster. This arbitrary meaning is inconsistent with teachings of the patents in suit and the general understanding of a POSA.

54. In fact, the patent record describes that a particular agent can act as a buffer ***and*** also perform other functions. For example, the ’074 Application—which I understand from Counsel is part of the intrinsic patent record—states that “***[b]uffering agents are used to adjust the pH*** of the pharmaceutical compositions.” (JA Ex. E, ’074 Application at A-101 (emphasis added).) Thus, the ’074 Application expressly supports my opinion that a “buffer” in the context of the patents in suit can also be a pH adjuster.

55. The patents in suit also disclose many agents that are suitable ***both*** as buffers ***and*** as pH adjusters. Such agents are highlighted in the table below:

Buffers	pH Adjusters
Buffers suitable for use in the pharmaceutical compositions described herein include, but are not limited to, pharmaceutically acceptable salts and acids of acetate, glutamate, citrate, tartrate, benzoate, lactate, histidine or other amino acids, gluconate, phosphate, malate, succinate, formate, propionate, and carbonate. (*See, e.g.*, JA Ex. A, '102 patent, col.4, ll.49-54 (emphasis added).)	In some embodiments, the premixed pharmaceutical compositions further comprise a pH adjuster. Suitable pH adjusters typically include at least an acid or a salt thereof, and/or a base or a salt thereof. Acids and bases can be added on an as needed basis in order to achieve a desired pH. For example, if the pH is greater than the desired pH, an acid can be used to lower the pH to the desired pH. Acids suitable for use in premixed pharmaceutical compositions include, but are not limited to, hydrochloric acid, phosphoric acid, citric acid, ascorbic acid, acetic acid, sulphuric acid, carbonic acid and nitric acid. In some embodiments, hydrochloric acid is used to adjust the pH. By way of another example, if the pH is less than the desired pH, a base can be used to adjust the pH to the desired pH. Bases suitable for use in premixed pharmaceutical compositions include, but are not limited to, sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, sodium citrate, sodium acetate, and magnesium hydroxide. (*See, e.g.*, JA Ex. A, '102 patent, col.5, ll.22-39 (emphasis added).)

As indicated in the table, the specifications describe that buffers include acids of acetate, citrate, phosphate, and carbonate. A POSA would understand that the acids of acetate, citrate, phosphate, and carbonate are acetic acid, citric acid, phosphoric acid, and carbonic acid, respectively. (Ex. 4, *Merriam-Webster Medical Desk Dictionary* (1996) at 6 (defining acetate as "a salt . . . of acetic acid"), at 143 (defining citrate as "a salt . . . of citric acid"), at 614 (defining phosphate as "a salt . . . of phosphoric acid"), at 112 (defining carbonate as "a salt . . . of carbonic acid").) These same acids are also described as pH adjusters in the specification. (JA Ex. A, '102 patent, col.5, ll.28-31.) Thus, according to the patents in suit, acetic acid, citric acid, phosphoric acid, and carbonic acid can all be ***both*** buffers ***and*** pH adjusters.

56. The patents in suit also describe that a buffer can include salts of negatively charged ions (*i.e.*, anions), including acetate, citrate, and carbonate. (*See, e.g.*, JA Ex. A, '102

patent, col.4 ll.49-54.) A POSA would understand that a positively charged ion (*i.e.*, a cation) can form salts with these anions (*e.g.*, a sodium cation can form sodium acetate, sodium citrate, and sodium carbonate, respectively). (Ex. 4, *Merriam-Webster Medical Desk Dictionary* (1996) at 6, 112, 143, and 614, respectively.) As shown in the table above in ¶ 55, these salts are also disclosed as pH adjusters in the patent specification. (JA Ex. A, '102 patent, col.5, ll.35-38.) Thus, again, the specification describes that for the pre-mixed aqueous solutions of the patents in suit, sodium citrate, sodium acetate, and sodium carbonate can all be ***both*** buffers ***and*** pH adjusters.

57. Chiesi's proposed construction is also consistent with the scientific description of a buffer "as a substance ***or mixture of substances*** . . . that in solution tends to stabilize hydrogen ion concentration by neutralizing within limits both acids and bases." (Ex. 4, *Merriam-Webster Medical Desk Dictionary* (1996) at 102 (emphasis added).) As described above in ¶ 47, pH is a measure of hydrogen ion concentration. And a POSA would understand that "neutralizing within limits both acids and bases" is another way of saying that the hydrogen ion concentration (reflected by the pH) is maintained within a specified range. Chiesi's proposed construction for the "buffer" claim term as "a system capable of maintaining the pH within an optimal pH range" allows for a substance or mixture of substances to stabilize pH, consistent with a POSA's general understanding of what a buffer is.

58. Ignoring these explicit disclosures of buffers that are also pH adjusters in the patent specification, Defendants' proposed construction for the claim term "buffer" excludes the possibility that a buffer can also be a pH adjuster. Defendants' proposed construction is, therefore, contradicted by the patents in suit (*i.e.*, by intrinsic evidence).

59. I have been informed by Counsel that it is impermissible for a claim construction to import exemplary embodiments or limitations from the specification into otherwise broad claim language in the absence of a clear requirement in the specification to do so. In my opinion, Defendants' proposed construction does just that because it requires that a buffer (i) be only a single "component" of the composition and (ii) maintain an optimal pH range "throughout the shelf-life of the product." The patent specification does not support adding these additional requirements into the construction for this claim term.

60. First, the specification expressly states that "the compositions may comprise multiple buffering agents," not just a single component. (JA Ex. A, '102 patent, col.13, ll.28-30.) Defendants' proposed construction—limiting buffer to a "[c]omponent of the composition (or aqueous solution) . . . ."—contradicts this explicit teaching of the specification. In my opinion, Defendants' proposed construction imports a specific embodiment (*i.e.*, with a single buffer component) to improperly narrow the meaning of the term "buffer" in the claims to only allow for a ***single component***.

61. Defendants' proposed construction is also not aligned with the knowledge a POSA. Indeed, as stated above, the *Merriam-Webster Medical Desk Dictionary* describes that buffers may include "a substance ***or mixture of substances*** . . . that in solution tends to stabilize hydrogen ion concentration by neutralizing within limits both acids and bases." (Ex. 4, *Merriam-Webster Medical Desk Dictionary* (1996) at 102 (emphasis added).) Thus, the extrinsic evidence also does not support the requirement in Defendants' proposed construction that a buffer has to be a ***single component*** of the composition.

62. Second, Defendants' proposed construction imports an additional requirement that a buffer maintain an optimal pH range "throughout the shelf-life of the product." I disagree

because the specification does not ***require*** maintaining optimal pH throughout the shelf-life of the product, as Defendants contend. (*See, e.g.*, JA Ex. A, '102 patent, col.4, ll.20-24.) Some claims of the patents in suit, for instance, require maintaining potency and/or impurity formation—both quantities influenced by pH—for only three months. (*Ibid.*, claims 8 and 9; JA Ex. C, '291 patent, claims 1 and 2; JA Ex. D, '524 patent, claims 1-18 and 23-28.) Another embodiment of the specification states that "the premixed pharmaceutical compositions provided herein are stable at room temperature for 6 months or longer due to the inclusion of a buffer capable of maintaining the pH within an optimal pH range." (JA Ex. A, '102 patent, col.3, ll.15-18.) But, also according to the specification, the shelf-life of the claimed inventions could be "at least 24 months." (*Ibid.*, col.3, ll.46-49.) Thus, a POSA would understand that a composition's shelf-life could exceed the three month or six month time periods disclosed by the patents in suit.

63. My opinion is supported by Cardene® I.V. Premixed Injection, a product covered by the claimed compositions of the patents in suit, which presently has an FDA-approved shelf-life of twenty four months. (Ex. 5, Cardene® I.V. Premixed Injection Ordering Information.) Moreover, when reviewing drug product shelf-life, the FDA recommends stability testing covering a minimum of twelve months. (Ex. 6, FDA Guidance for Industry "Q1A(R2) Stability Testing of New Drug Substances and Products," p. 10.) The twenty four-month shelf-life of Cardene® I.V. Premixed Injection and twelve months of shelf-life testing required by the FDA, therefore, both significantly exceed the three months and six months time periods disclosed by the patents in suit. This fact further supports my opinion that Defendants' proposed construction imports a specific embodiment (*i.e.*, shelf-life) from the specification to impermissibly narrow the meaning of the claim term "buffer" and is contradicted by the specification.

* * *

I declare under penalty of perjury that the foregoing, to the best of my knowledge, is true and correct.

Dated: February 20, 2015

Alexander M. Klibanov, Ph.D.

APPENDIX A

Curriculum vitae

ALEXANDER M. KLIBANOV

Date and Place of Birth: July 15, 1949, in Moscow (Russia)

Nationality: Naturalized U.S. Citizen (1983)

Education:

1974	Ph.D. in Chemical Enzymology, Moscow University
1971	M.S. in Chemistry, Moscow University

Honors:

2007-11 and 2014-	Novartis Chair Endowed Professorship, MIT
2012-13	Roger and Georges Firmenich Endowed Professorship, MIT
2011	MIT Biological Engineering Senior Class Faculty Award
2006	Distinguished GRUM Lecturer in Drug Discovery & Development, University of Montreal (Canada)
2004	UNAM Distinguished Lecturer, National University of Mexico (Mexico City)
2001	Walter Enz Lecturer in Pharmaceutical Chemistry, University of Kansas
2001	Elected a Corresponding Fellow of the Royal Society of Edinburgh (Scotland's National Academy of Science and Letters)
2000	Merck Distinguished Lecturer, Rutgers University
2000	Top 20 *Biotechnology & Bioengineering* Papers of the Last Forty Years
1998	Robert Lutz Lecturer, University of Virginia
1996	Perkin-Elmer Distinguished Lecturer, University of Pittsburgh
1995	Elected to the National Academy of Sciences of the U.S.A.
1995	Nathan O. Kaplan Memorial Lecturer in Biological Chemistry, University of California at San Diego
1994	R.W. Johnson PRI Lecturer, Pharmaceutical Research Institute
1994	Warren McCabe Lecturer, North Carolina State University
1993	Elected to the National Academy of Engineering of the U.S.A.
1993	Arthur C. Cope Scholar Award of the American Chemical Society
1993	Biotechnology Divisional Lectureship Award of the Institute of Food Technologists
1992	Charles Sabat Lecturer, Rutgers University
1992	Elected a Founding Fellow of the American Institute for Medical and Biological Engineering
1992	Louis C. Jordy Research Scholar Lecturer, Drew University
1991	International Enzyme Engineering Award
1991	Marvin J. Johnson Award of the American Chemical Society
1990	Monsanto Lecturer, Ohio State University
1990	NRC Distinguished Lecturer, Academia Sinica (Taiwan)
1989	Ipatieff Prize of the American Chemical Society
1989	Backer Lecturer, Groningen University (Holland)
1988	Dow Lecturer, University of Ottawa (Canada)
1987	Distinguished Scholar Lecturer, Hope College
1986	Leo Friend Award of the American Chemical Society
1984	Who's Who in Frontier Science and Technology

1984	Sohio Lecturer, Case Western Reserve University
1982	American Men and Women of Science
1981-1983	Henry L. Doherty Career Development Professorship, MIT
1975	U.S.S.R. Ministry of Higher Education Prize

Professional Experience:

2007-11 and 2014-	Novartis Chair Endowed Professor of Chemistry and Bioengineering, MIT
2012-2013	Roger and Georges Firmenich Professor of Natural Products Chemistry Department of Chemistry, MIT
2000-present	Professor of Bioengineering Department of Biological Engineering, MIT
1988-present	Professor of Chemistry Department of Chemistry, MIT
1987-1988	Professor of Applied Biochemistry Department of Applied Biological Sciences, MIT
1983-1987	Associate Professor of Applied Biochemistry Department of Applied Biological Sciences (formerly Department of Nutrition and Food Science), MIT
1979-1983	Assistant Professor of Applied Biochemistry Department of Nutrition and Food Science, MIT
1977-1979	Postdoctoral Associate, Department of Chemistry University of California at San Diego
1974-1977	Research Chemist Department of Chemistry, Moscow University

Current Journal Editorial/Advisory Boards:

"Biocatalysis and Biotransformation", "Applied Biochemistry and Biotechnology", "Central European Journal of Chemistry", "Biotechnology Progress", "Biotechnology & Bioengineering", "Microbial Biotechnology", "Open Journal of Pharmacology", "Nanocarriers", "Journal of Antivirals and Antiretrovirals", "Open Access Academic Books in Chemistry", "Journal of Biological Chemistry and Molecular Pharmacology", "Recent Patents in Biotechnology"

Professional Societies:

U.S. National Academy of Sciences, U.S. National Academy of Engineering, American Chemical Society, Society for Applied Microbiology

Current Research Interests:

Enzyme chemistry and biotechnology
Medicinal and formulation chemistry
Protein drug delivery
Antimicrobial polymers
Enzymes as stereoselective catalysts in organic syntheses
Stabilization and formulation of macromolecular pharmaceuticals

Publications:

1. Varfolomeyev, S.D., Klibanov, A.M., Berezin, I.V. 1971. Light-initiated enzymic activity caused by photostereoisomerization of *cis*-4-nitrocinnamoyl-α-chymotrypsin. FEBS Lett. 15: 118 -120.

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308. Tandon, A., Sharma, A., Rodier, J.T., Klibanov, A.M., Rieger, F.G., Mohan, R.R. 2013. BMP7 gene transfer via gold nanoparticles into stroma inhibits corneal fibrosis *in vivo*. PLOS ONE

8(6): e66434, 1-9.

309. Liu, H., Kim, Y., Mello, K., Lovaasen, J., Shah, A., Rice, N., Yim, J.H., Pappas, D., Klibanov, A.M. 2014. Aerosol-assisted plasma deposition of hydrophobic polycations makes surfaces highly antimicrobial. Appl. Biochem. Biotechnol. 172: 1254-1264.

310. Zhu, A., Liu, H.K., Long, F., Su, E., Klibanov, A.M. 2015. Biocidal action of electric current applied to composite membranes containing carbon nanotubes. Appl. Biochem. Biotechnol. 175: 666-676.

311. Liu, K., Elkin, I., Chen, J., Klibanov, A.M. 2015. Why do some immobilized *N*-alkylated polyethylenimines far surpass others in inactivating influenza viruses? Biomacromolecules 16: 351-356.

312. Su, E., Klibanov, A.M. 2014. Low-transition-temperature mixtures (LTTMs) for dissolving proteins and for drug formulation. Appl. Biochem. Biotechnol., submitted.

313. Li, D., He, M., Lewis, K., Klibanov, A.M., Gu, A.Z. The role of environmental contaminants in selecting the antibiotic resistance. Nature Biotechnol., submitted.

Patents:

1. Klibanov, A.M., Langer, R.S. Methods of decreasing the hydrophobicity of fibroblast and other interferons. U.S. Patent No. 4,414,147; November 8, 1983.

2. Klibanov, A.M., Kirchner, G. Enzymatic production of optical isomers of 2-halopropionic acids. U.S. Patent No. 4,601,987; July 22, 1986.

3. Klibanov, A.M. Removal of combined organic substances from aqueous solutions. U.S. Patent No. 4,623,465; November 18, 1986.

4. Klibanov, A.M. Enzymatic resolution of racemic mixtures of hydroxy compounds. U.S. Patent No. 4,659,671; 1987.

5. Klibanov, A.M., Dordick, J.S. Enzymatic temperature change indicator. U.S. Patent No. 4,826,762; May 2, 1989.

6. Dorval, B.L., Denham, L., Klibanov, A.M. Radial flow assay, delivering membrane, test kit, and methods. U.S. Patent No. 5,547,833; August 20, 1996.

7. Dorval, B.L., Denham, L., Klibanov, A.M. Detection reagent, particle, and immunoassay method. U.S. Patent No. 5,561,045; October 1, 1996.

8. Dorval, B.L., Chow, M., Klibanov, A.M. Stabilized vaccine compositions. U.S. Patent No. 5,618,539; April 8, 1997. European Patent No. 0 487 632; March 4, 1998.

9. Klibanov, A.M., Lewis, K., Ferrante, A.A., Coyle, C.L., Zylstra, G., Logan, M.S.P., Grossman, M.J. Solvent-resistant microorganisms. U.S. Patent No. 5,807,735; September 15, 1998.

10. Gresser, J.D., Trantolo, D.J., Langer, R., Klibanov, A.M., Wise, D.L. Material for buffered resorbable internal fixation devices and method for making the same. U.S. Patent No. 5,817,328; October 6, 1998.

11. Hekal, I.M., Langer, R.S., Klibanov, A.M., Mathiowitz, E. Monolithic polymer composition having a water absorption material. U.S. Patent No. 6,174,952; January 16, 2001.

12. Gresser, J.D., Trantolo, D.J., Langer, R., Lewandrowski, K.-U., Klibanov, A.M., Wise, D.L. Resorbable interbody spinal fusion devices. U.S. Patent No. 6,241,771; June 5, 2001.

13. Trantolo, D.J., Langer, R., Klibanov, A.M., Wise, D.L. Buffered resorbable internal fixation devices and methods for making material therefor. U.S. Patent No. 6,419,945; July 16, 2002.

14. Gresser, J.D., Trantolo, D.J., Langer, R., Lewandrowski, K.-U., Klibanov, A.M., Wise, D.L. Method of making biodegradable interbody spinal fusion devices. U.S. Patent No. 6,548,002; April 15, 2003.

15. Klibanov, A.M. Nonaqueous solutions and suspensions of macromolecules for pulmonary delivery. U.S. Patent No. 6,660,715; December 9, 2003.

16. Tiller, J.C., Lewis, K., Liao, C.-J., Klibanov, A.M. Antimicrobial polymeric surfaces. U.S. Patent No. 7,151,139; December 19, 2006.

17. Hirsh, J.C., Fleming, A.B., Rariy, R.V., Klibanov, A.M. Abuse-deterrent pharmaceutical formulations. U.S. Patent No. 8,449,909; May 28, 2013.

18. Kamiya, N., Klibanov, A.M. Controlled drug release formulations containing polyion complexes. U.S. Patent Appl. Publ. No. 2004224024, 2004.

19. Rariy, R.V., Fleming, A.B., Hirsh, J.C., Klibanov, A.M. Abuse-deterrent pharmaceutical compositions of opioids and other drugs. U.S. Patent No. 8,557,291; October 15, 2013.

20. Fleming, A.B., Rariy, R.V., Hirsh, J.C., Klibanov, A.M. Sustained release compositions of drugs. U.S. Patent Appl. Publ. No. 2008/0260819; October 23, 2008.

21. Haldar, J., Alvarez de Cienfuegos, L., Klibanov, A.M., Chen, J. Bi-functional polymer-attached inhibitors of influenza virus. PCT Intl. Appl. WO 2009/032605, 2012.

22. Haldar, J., Chen, J., Klibanov, A.M. Non-leaching virucidal coatings, pending.

23. Haldar, J., An, D., Álvarez de Cienfuegos, L., Chen, J., Klibanov, A.M. Polymeric coatings that inactivate viruses and bacteria. U.S. Patent Appl. Publ. No. 2010/0136072; June 3, 2010.

24. Pedersen, M., Stanley, M., Gouin, S., Klibanov, A.M, Hsu, B.B. Antimicrobial quat coating on fabrics. PCT Intl. Appl. WO 2012/06561, 2012.

25. Schaer, P.T., Hsu, B.B., Stewart, S., Klibanov, A.M. Hydrophobic polycationic coatings that inhibit biofilm formation on orthopedic implants and support healing during infection, pending.

26. Schaer, P.T., Stewart, S., Klibanov, A.M. Antibacterial coatings that inhibit biofilm formation on implants. U.S. Patent Appl. Publ. No. 2013/0110237 A1, 2013.

Invited Lectures:

1. Gordon Conference on Immobilized Enzymes, Complexes, and Cells (Plymouth, NH). August 1978.
2. 5th International Conference on Enzyme Engineering (Henniker, NH). August 1978.
3. Miles Laboratories (Elkhart, IN). February 1980.
4. Gordon Conference on Immobilized Species (Henniker, NH). August 1980.
5. Novo Laboratories (Wilton, CT). October 1980.
6. Corning Glass Works Co. (Corning, NY). October 1980.
7. Stauffer Chemical Co. (Dobbs Ferry, NY). December 1980.
8. DuPont Experimental Station (Wilmington, DE). January 1981.
9. Dow Chemical Co. (Wayland, MA). April 1981.
10. Cetus Corp. (Berkeley, CA). April 1981.
11. Exxon Research & Engineering Co. (Linden, NJ). April 1981.
12. Meeting of the American Solar Energy Society (Philadelphia, PA). May 1981.
13. 6th International Conference on Enzyme Engineering (Kashikojima, Japan). September 1981.
14. Genex Corp. (Rockville, MD). October 1981.
15. ILP Symposium for Senior Executives (London, England). November 1981.
16. California Institute of Technology (Pasadena, CA). December 1981.
17. Symposium of the American Society for Microbiology (Atlanta, GA). March 1982.
18. Kodak Research Center (Rochester, NY). March 1982.
19. Repligen Corp. (Cambridge, MA). April 1982.
20. Symposium on the Biological Basis of New Developments in Biotechnology (Minneapolis, MN). May 1982.
21. Meeting of the Biochemical Society (Oxford, England). July 1982.
22. Meeting of the American Chemical Society (Kansas City, MO). September 1982.

23. Rotenburger Symposium on Enzyme Technology (Kassel, Germany). September 1982.
24. Genetics Institute (Boston, MA). September 1982.
25. Meeting of the American Institute of Chemical Engineers (Los Angeles, CA). November 1982.
26. G.D. Searle Co. (Chicago, IL). October 1982.
27. Halcon International Research Center (Montvale, NJ). October 1982.
28. International Workshop on Immobilized Enzymes and Cells (Bangkok, Thailand). December 1982.
29. Amoco Research Center (Naperville, IL). January 1983.
30. University College London (London, England). May 1983.
31. International Conference on Biotechnology Biotech '83 (London, England). May 1983.
32. Tufts University Workshop on Immobilized Enzymes and Proteins (Medford, MA). June 1983.
33. Gordon Conference on Organic Reactions and Processes (New Hampton, NH). July 1983.
34. Symposium “Biocatalysis: New Discoveries and Uses”, Meeting of the American Society for Industrial Microbiology (Sarasota, FL). August 1983.
35. Monsanto Co. (St. Louis, MO). September 1983.
36. Pasteur Biosciences ‘83 Conference (Paris, France). September 1983.
37. 7th International Conference on Enzyme Engineering (White Haven, PA). September 1983.
38. University of Iowa (Iowa City, IA). October 1983.
39. CPC Moffett Technical Center (Summitt-Argo, IL). December 1983.
40. General Foods Co. (Dobbs Ferry, NY). December 1983.
41. U.S. National Bureau of Standards (Gaithersburg, MD). April 1984.
42. Millipore Corp. (Bedford, MA). April 1984.
43. Technical University of Munich (Munich, F.R.G.). May 1984.
44. Danish Academy of Technical Sciences (Copenhagen, Denmark). May 1984.
45. Novo International Biotechnology Symposium (Copenhagen, Denmark). May 1984.
46. CRA Scientific Conference (St. Charles, IL). June 1984.

47. Gordon Conference on Immobilized Species in Biotechnology (Plymouth, NH). August 1984.
48. Meeting of the American Chemical Society (Philadelphia, PA). August 1984.
49. International Biotechnology Conference Biotech '84 (Washington, DC). September 1984.
50. Staley Manufacturing Co. (Decatur, IL). October 1984.
51. Case Western Reserve University (Cleveland, OH). October 1984.
52. IMC Corp. (Terre Haute, IN). October 1984.
53. Syracuse University (Syracuse, NY). November 1984.
54. National University of Mexico (Mexico City, Mexico). November 1984.
55. National Starch & Chemical Corp. (Bridgewater, NJ). November 1984.
56. Mead Corp. (Chillicothe, OH). November 1984.
57. Hebrew University of Jerusalem (Jerusalem, Israel). November 1984.
58. U.S. Army Chemical R&D Center (Aberdeen Proving Ground, MD). December 1984.
59. Allied Corp. (Morristown, NJ). December 1984.
60. Bristol Laboratories (Syracuse, NY). January 1985.
61. University of Rochester (Rochester, NY). January 1985.
62. G.D. Searle Co. (Chicago, IL). February 1985.
63. Wellcome Research Laboratories (Research Triangle Park, NC). February 1985.
64. UCLA Symposium on Protein Structure, Folding and Design (Keystone, CO). April 1985.
65. International Conference on Application of Biocatalysts in Organic Synthesis (Noordwijkerhout, Holland). April 1985.
66. Guido Donegani Research Institute (Novara, Italy). April 1985.
67. Hoffmann-LaRoche Co. (Basel, Switzerland). April 1985.
68. Pittsburgh-Cleveland Catalysis Society Meeting (Pittsburgh, PA). May 1985.
69. Ethyl Corp. (Baton Rouge, LA). May 1985.
70. Stony Brook Symposium on Protein Engineering (Stony Brook, NY). May 1985.
71. Amgen Corp. (Thousand Oaks, CA). June 1985.

72. Gordon Conference on Applied Microbiology (New London, NH). August 1985.

73. International Congress of Biochemistry (Amsterdam, Holland). August 1985.

74. IUPAC Congress (Manchester, England). September 1985.

75. International Enzyme Engineering Conference (Helsingor, Denmark). September 1985.

76. Biotechnica '85 (Hannover, West Germany). October 1985.

77. Biotec 85 (Dusseldorf, West Germany). October 1985.

78. Smith Kline & French Co. (Philadelphia, PA). November 1985.

79. Exxon Corporate Research (Anandale, NJ). December 1985.

80. Pennsylvania State University (University Park, PA). December 1985.

81. Georgetown University (Washington, DC). February 1986.

82. Columbia University (New York, NY). February 1986.

83. Upjohn Co. (Kalamazoo, MI). February 1986.

84. UNIDO Workshop on Biotechnology (Trieste, Italy). March 1986.

85. Enericherche (Monterotondo, Italy). March 1986.

86. EEC Biomolecular Engineering Meeting (Compiegne, France). April 1986.

87. ACS Conference on Chemical Aspects of Biotechnology (Gaithersburg, MD). May 1986.

88. Biotech '86 Europe International Conference (London, England). May 1986.

89. IUPAC International Symposium on Organic Chemistry in Technological Perspective (Jerusalem, Israel). June 1986.

90. University of Tel-Aviv (Ramat-Aviv, Israel). June 1986.

91. Annual Meeting of the Canadian Biochemical Society (Guelph, Canada). June 1986.

92. International Symposium on Biologically Engineered Polymers (Cambridge, England). July 1986.

93. TNO Institute of Applied Chemistry (Zeist, The Netherlands). August 1986.

94. IUPAC International Symposium on the Chemistry of Natural Products (The Hague, The Netherlands). August 1986.

95. American Chemical Society National Meeting (Anaheim, CA). September 1986.

96. Catalytica Annual Science and Technology Symposium (San Jose, CA). September 1986.

97. International Conference on Enzyme Engineering (Cambridge, England). September 1986.

98. Ohio State University (Columbus, OH). October 1986.

99. Michigan State University (Lansing, MI). October 1986.

100. Biotechnology Process Engineering Symposium (Cambridge, MA). October 1986.

101. University of Delaware (Newark, DE). November 1986.

102. American Red Cross Blood Research Institute (Bethesda, MD). November 1986.

103. International Symposium on Biocatalysis in Non-Aqueous Solvents (Wageningen, The Netherlands). December 1986.

104. University of Trondheim (Trondheim, Norway). December 1986.

105. Colgate-Palmolive Research Center (Piscataway, NJ). January 1987.

106. International Paper Co. (Tuxedo Park, NY). January 1987.

107. University of Massachusetts (Amherst, MA). February 1987.

108. American Society for Microbiology Biocatalysis Symposium (Atlanta, GA). March 1987.

109. Hope College (Holland, MI). March 1987.

110. Pfizer Corporate Research Center (Groton, CT). April 1987.

111. OBBS Symposium on Protein Engineering (Ottawa, Canada). April 1987.

112. University of Texas (Austin, TX). April 1987.

113. Florida Catalysis Conference (Palm Coast, FL). May 1987.

114. PPG Industries (Barberton, OH). May 1987.

115. Abbott Laboratories (North Chicago, IL). May 1987.

116. American Oil Chemists Society Symposium on Lipases (New Orleans, LA). May 1987.

117. Argonne National Laboratory (Argonne, IL). June 1987.

118. Canadian Chemical Conference (Quebec City, Canada). June 1987.

119. Squibb Co. (New Brunswick, NJ). June 1987.

120. FEBS Annual Meeting (Ljubljana, Yugoslavia). July 1987.

121. L'Oreal Research Institute (Paris, France). July 1987.

122. International Symposium on Biointeractions (Cambridge, England). July 1987.

123. Eli Lilly Co. (Indianapolis, IN). August 1987.

124. Upjohn Co. (Kalamazoo, MI). September 1987.

125. International Enzyme Engineering Conference (Santa Barbara, CA). October 1987.

126. Shell Development Co. (Houston, TX). October 1987.

127. DuPont Experimental Station (Wilmington, DE). October 1987.

128. University of Helsinki (Helsinki, Finland). November 1987.

129. International Conference on Bioreactors and Biotransformations (Gleneagles, Scotland). November 1987.

130. Sandoz Co. (Basel, Switzerland). November 1987.

131. University of Waterloo (Waterloo, Canada). December 1987.

132. Norwegian Biochemical Society Annual Meeting (Bejito, Norway). January 1988.

133. Rutgers University (New Brunswick, NJ). February 1988.

134. University of Ottawa (Ottawa, Canada). February 1988.

135. Boston Biomedical Research Institute (Boston, MA). March 1988.

136. Princeton University (Princeton, NJ). March 1988.

137. Royal Society of Chemistry Meeting (Kent, England). April 1988.

138. Stanford University (Stanford, CA). May 1988.

139. University of Graz (Graz, Austria). May 1988.

140. Belgian Organic Chemistry Symposium (Ghent, Belgium). May 1988.

141. Dow Chemical Co. (Midland, MI). May 1988.

142. Michigan State University (Lansing, MI). May 1988.

143. American Chemical Society Meeting (Toronto, Canada). June 1988.

144. Proctor & Gamble Co. (Cincinnati, OH). June 1988.

145. International Congress of Biochemistry (Prague, Czechoslovakia). July 1988.

146. International Biotechnology Symposium (Paris, France). July 1988.

147. Gordon Conference on Catalysis (Newport, RI). August 1988.

148. Conference on Biocatalytic Synthesis of Organic Compounds (Saratoga, NY). August 1988.

149. International Symposium on Thermodynamics Applied to Biological Systems (Santa Margherita, Italy). September 1988.

150. Cornell University (Ithaca, NY). September 1988.

151. Eastman Kodak Co. (Kingsman, TN). September 1988.

152. Symposium on Biotechnology Challenges in the Food Industry (Williamsburg, VA). October 1988.

153. University of California at Irvine (Irvine, CA). October 1988.

154. UCSF Symposium on Protein and Drug Design (San Francisco, CA). October 1988.

155. Boston University (Boston, MA). October 1988.

156. Wayne State University (Detroit, MI). November 1988.

157. Kyoto Symposium on Frontiers in Biocatalysis (Kyoto, Japan). November 1988.

158. Rohm & Haas Co. (Spring House, PA). January 1989.

159. Block Drug Co. (Jersey City, NJ). January 1989.

160. State University of New York (Albany, NY). March 1989.

161. Scripps Clinic and Research Foundation (La Jolla, CA). April 1989.

162. Texas A&M University (College Station, TX). May 1989.

163. University of Texas (Austin, TX). May 1989.

164. International Congress of Food Engineering (Cologne, F.R.G.). May 1989.

165. University of Groningen (Groningen, The Netherlands). June 1989.

166. Gordon Conference on Enzymes, Coenzymes, and Metabolic Pathways (Meridan, NH). July 1989.

167. American Peptide Symposium (La Jolla, CA). July 1989.

168. International Symposium on Prospects in Protein Engineering (Haren, The Netherlands). August 1989.

169. Connaught Laboratories (Toronto, Canada). September 1989.

170. University of Georgia (Athens, GA). October 1989.

171. Spanish National Congress of Biochemistry (Alicante, Spain). October 1989.

172. Symposium on Receptor- and Enzyme-Based Drug Design (Chapel Hill, NC). October 1989.

173. Wesleyan University (Middletown, CT). November 1989.

174. University of Wisconsin (Madison, WI). February 1990.

175. Merck Sharp & Dohme Research Laboratories (Rahway, NJ). February 1990.

176. International Symposium on Biochemical Engineering (Stuttgart, F.R.G.). March 1990.

177. University of Geneva (Geneva, Switzerland). March 1990.

178. University of Lausanne (Lausanne, Switzerland). March 1990.

179. University of Bern (Bern, Switzerland). March 1990.

180. University of Fribourg (Fribourg, Switzerland). March 1990.

181. International Conference on Protein Stability (Cambridge, England). March 1990.

182. AFRC Institute of Food Research (Reading, England). March 1990.

183. Lehigh University (Bethlehem, PA). April 1990.

184. Biotechnology Research Institute (Montreal, Canada). April 1990.

185. Ohio State University (Columbus, OH). April 1990.

186. Pharmaceutical Manufacturers Association Annual Meeting (St. Louis, MO). April 1990.

187. International Conference on Industrial Use of Enzymes (Chicago, IL). May 1990.

188. Korea Advanced Institute of Science and Technology (Seoul, Korea). June 1990.

189. Academia Sinica and National Taiwan University (Taipei, Taiwan). June 1990.

190. Gordon Conference on Biocatalysis (Plymouth, NH). June 1990.

191. IUPAC Conference on Organic Synthesis (Helsinki, Finland). July 1990.

192. International Conference on Solution Chemistry (Ottawa, Canada). August 1990.

193. Gordon Conference on Biomolecular Recognition (Plymouth, NH). August 1990.

194. University of Naples (Naples, Italy). September 1990.

195. International Conference on Water and Life (Crans-sur-Sierre, Switzerland). September 1990.

196. International Symposium on Thermodynamic Basis of Protein Structure and Function (Kansas City, MO). October 1990.

197. Johns Hopkins University (Baltimore, MD). October 1990.

198. Institute of Medicine Workshop on Microheterogeneity of Biological Macromolecules (Arlington, VA). November 1990.

199. U.S.-Japan Biotechnology Conference (Honolulu, HI). January 1991.

200. Ciba-Geigy Corp. (Summit, NJ). February 1991.

201. City University of New York (New York, NY). March 1991.

202. Rensselaer Polytechnic Institute (Troy, NY). March 1991.

203. Bristol-Myers Squibb Co. (Wallingford, CT). April 1991.

204. British Biochemical Society Meeting (Reading, England). April 1991.

205. University of California at Berkeley (Berkeley, CA). April 1991.

206. California Institute of Technology (Pasadena, CA). April 1991.

207. Merck, Sharp & Dohme Research Laboratories (West Point, PA). May 1991.

208. Bristol-Myers Squibb Research Institute (Princeton, NJ). May 1991.

209. International Conference on Biocatalysis (Orlando, FL). June 1991.

210. U.S. Army Research, Development and Engineering Center (Natick, MA). July 1991.

211. Gordon Conference on Natural Products (Plymouth, NH). July 1991.

212. Lederle-Praxis Biologicals Co. (Sanford, NC). July 1991.

213. International Biochemistry Congress (Jerusalem, Israel). August 1991.

214. American Chemical Society Meeting (New York, NY). August 1991.

215. International Enzyme Engineering Conference (Kona, HI). September 1991.

216. University of Lowell (Lowell, MA). October 1991.

217. Rutgers University (Piscataway, NJ). November 1991.

218. International Symposium on Enzymes in Organic Synthesis (New Delhi, India). January 1992.

219. International BioSymposium Nagoya '92 (Nagoya, Japan). January 1992.

220. International Symposium on Biomolecules in Organic Solvents (Taxco, Mexico). February 1992.

221. Rockefeller University (New York, NY). March 1992.

222. Symposium on Molecular Chirality of the Pharmaceutical Society of Japan (Tokyo, Japan). April 1992.

223. Conference on Enzymes in Organic Chemistry of the Dutch Chemical Society (Wageningen, The Netherlands). April 1992.

224. International Symposium on Bioprocessing of Coal (Clearwater Beach, FL). May 1992.

225. Exxon Workshop on New Leads in Coal Depolymerization (Montgomery, TX). May 1992.

226. Italian Symposium on Biochemical Biotechnology (Capri, Italy). June 1992.

227. Gordon Conference on Biocatalysis (Meriden, NH). July 1992.

228. FEBS Meeting (Dublin, Ireland). August 1992.

229. International Biotechnology Symposium (Washington, DC). August 1992.

230. International Symposium Bio Japan '92 (Yokohama, Japan). August 1992.

231. Texas College of Osteopathic Medicine (Fort Worth, TX). October 1992.

232. Rutgers University (Newark, NJ). October 1992.

233. Schering-Plough Co. (Bloomfield, NJ). November 1992.

234. International Symposium ISOPOW-V: *Properties of Water in Foods* (Peniscola, Spain). November 1992.

235. Carlsberg Laboratory (Copenhagen, Denmark). November 1992.

236. International Food Technology Conference (The Hague, The Netherlands). November 1992.

237. Singapore Institute of Standards and Industrial Research (Singapore). November 1992.

238. Drew University (Madison, NJ). December 1992.

239. Northeastern University (Boston, MA). January 1993.

240. Ciba Corning Diagnostics Corp. (Irvine, CA). January 1993.

241. University of Kansas (Lawrence, KS). January 1993.

242. 6th International Symposium on Recent Advances in Drug Delivery Systems (Salt Lake City, UT). February 1993.

243. Pennsylvania State University (University Park, PA). March 1993.

244. Northwestern University (Evanston, IL). March 1993.

245. International Symposium on Technologies for the Production of Enantiomerically Pure Chemicals (Amelia Island, FL). March 1993.

246. Gordon Conference on Bioanalytical Sensors (Ventura, CA). March 1993.

247. Pharmaceutical Manufacturers Association Analytical R&D/Pharmaceutical Development Subsections Joint Annual Meeting (Lake Buena Vista, FL). April 1993.

248. University of Massachusetts Symposium on Breakthrough Technologies: *Paradigms for a New Century* (Amherst, MA). May 1993.

249. Parke-Davis Corp. (Ann Arbor, MI). May 1993.

250. NutraSweet Co. (Mt. Prospect, IL). June 1993.

251. IGT/GRI Workshop on Novel Concepts for the Production of Regio- and Stereospecific Compounds (Chicago, IL). June 1993.

252. Northeast Regional Meeting of the American Chemical Society (Boston, MA). June 1993.

253. Institute of Food Technologists' Biotechnology Meeting (Chicago, IL). July 1993.

254. Annual Meeting of Department of Energy's Biological and Chemical Technology Research Program Principal Investigators (Tiburon, CA). July 1993.

255. Allied-Signal Corp. (Des Plains, IL). July 1993.

256. American Chemical Society Meeting (Chicago, IL). August 1993.

257. University of Illinois at Urbana-Champaign (Urbana, IL). September 1993.

258. International Enzyme Engineering Conference (Deauville, France). September 1993.

259. Queens College (Flushing, NY). November 1993.

260. Exxon Chemical Research Meeting (Galveston, TX). November 1993.

261. Hoffmann-LaRoche Co. (Nutley, NJ). December 1993.

262. U.S.-Japan Symposium on Drug Delivery (Maui, HI). December 1993.

263. North Dakota State University (Fargo, ND). February 1994.

264. Annual Meeting of the American Institute for Medical and Biological Engineering (Washington, DC). March 1994.

265. Rhone-Poulenc Rorer Symposium on Visions in Chemistry (Collegeville, PA). May 1994.

266. International Flavors & Fragrances R&D (Union Beach, NJ). May 1994.

267. Istituto degli Ormoni (Milan, Italy). June 1994.

268. Gordon Conference on Enzymes, Coenzymes, and Metabolic Pathways (Meriden, NH). July 1994.

269. Annual Meeting of Department of Energy's Biological and Chemical Technology Research Program Principal Investigators (Denver, CO). July 1994.

270. William S. Johnson Symposium in Organic Chemistry (Stanford, CA). October 1994.

271. R.W. Johnson Pharmaceutical Research Institute (Spring House, PA). October 1994.

272. International Congress of Biochemical Engineering (Mexico City, Mexico). October 1994.

273. National University of Mexico (Mexico City, Mexico). October 1994.

274. DuPont Merck Pharmaceutical Co. (Deepwater, NJ). December 1994.

275. Symposium on Therapeutic Protein Production and Processing (Cambridge, MA). January 1995.

276 International Symposium on Biocatalysts for Flavor Production, BioFlavour '95 (Dijon, France). February 1995.

277. Institut Pasteur (Paris, France). February 1995.

278. Florida State University (Tallahassee, FL). March 1995.

279. Abbott Laboratories (North Chicago, IL). March 1995.

280. University of Maryland, Baltimore County (Baltimore, MD). March 1995.

281 University of California at San Diego (La Jolla, CA). April 1995.

282. Great Lakes Regional Meeting of the American Chemical Society (LaCrosse, WI). June 1995.

283. Gordon Conference on Bioorganic Chemistry (Andover, NH). June 1995.

284. Annual Meeting of Department of Energy's Biochemical and Chemical Technology Research Principal Investigators (Albuquerque, NM). July 1995.

285. International Symposium "Biocatalysis-95" (Suzdal, Russia). August 1995.

286. International Enzyme Engineering Conference (San Diego, CA). October 1995.

287. Symposium on Biomacromolecules: *From 3-D Structure to Applications* (Pasco, WA). October 1995.

288. Enzymol International Inc. (Columbus, OH). December 1995.

289. International Symposium Pacifichem '95 (Honolulu, HI). December 1995.

290. 3rd U.S.-Japan Symposium on Drug Delivery (Maui, HI). December 1995.

291. New England Section of the Society for Industrial Microbiology (Cambridge, MA). February 1996.

292. Brown University (Providence, RI). February 1996.

293. University of Pittsburgh (Pittsburgh, PA). February 1996.

294. Food Research Institute (Reading, England). March 1996.

295. International Symposium Chiral USA '96 (Boston, MA). May 1996.

296. BP Catalyst Colloquium (Uxbridge, England). June 1996.

297. International Symposium on Homogeneous Catalysis (Princeton, NJ). August 1996.

298. Juan March Foundation's International Workshop on Novel Biocatalysts (Madrid, Spain). March 1997.

299. University of Kentucky (Lexington, KY). April 1997.

300. Gordon Conference on Organic Reactions and Processes (Henniker, NH). August 1997.

301. Novo Nordisk Symposium on Protein Stability (Klampenborg, Denmark). August 1997.

302. International Enzyme Engineering Conference (Beijing, China). October 1997.

303. Biogen Inc. (Cambridge, MA). December 1997.

304. INBIO Europe'98 Conference on Advances in Industrial Biocatalysis (Amsterdam, The Netherlands). February 1998.

305. International Symposium on Stability and Stabilization of Biocatalysts (Córdoba, Spain). April 1998.

306. International Symposium on Protein Structure, Stability and Folding: *Fundamental and Medical Aspects* (Moscow, Russia). June 1998.

307. International Conference on Protein Stabilization (Leeds, England). June 1998.

308. University of Virginia (Charlottesville, VA). September 1998.

309. Danish Biotechnology Conference (Vejle, Denmark). May 1999.

310. International Conference on Biocatalysis and Biotransformation Biotrans '99 (Giardini Naxos, Italy). September 1999.

311. Annual Meeting of the American Association of Pharmaceutical Scientists (New Orleans, LA). November 1999.

312. Brandeis University (Waltham, MA). November 1999.

313. Rutgers University (Piscataway, NJ). March 2000.

314. Chiral USA 2000 Conference (Boston, MA). May 2000.

315. Land O'Lakes Conference on Solid-State Reactivity in Pharmaceutical Systems (Merrimac, WI). June 2000.

316. Agouron Pharmaceuticals Inc. (San Diego, CA). July 2000.

317. U.S. Patent and Trademark Office Technology Fair (Arlington, VA). July 2000.

318. 23rd Gulf Coast Chemistry Conference (Pensacola, FL). September 2000.

319. Avon Products (Suffern, NY). November 2000.

320. Procter & Gamble Co. (Cincinnati, OH). November 2000.

321. Flamel Technologies (Venissieux, France). December 2000.

322. BioVision 2001 International Conference (Lyon, France). February 2001.

323. 9th Baxter Science and Technology Symposium (Hyland, IL). May 2001.

324. International Symposium on Applications of Enzymes in Chemical and Biological Defense (Orlando, FL). May 2001.

325. International Conference on Applied Biocatalysis (Trondheim, Norway). June 2001.

326. PPG Industries (Allison Park, PA). August 2001.

327 University of Kansas (Lawrence, KS). August 2001.

328. Alkermes Inc. (Cambridge, MA). October 2001.

329. 6th U.S.-Japan Symposium on Drug Delivery Systems (Maui, HI). December 2001.

330. Acambis Inc. (Cambridge, MA). January 2002.

331. Baxter BioScience Co. (Duarte, CA). January 2002.

332. International Symposium on Challenges in Drug Discovery and Development in the 21st Century (Kolkata, India). March 2002.

333. National Institute of Standards and Technology (Gaithersburg, MD). April 2002.

334. Albany Molecular Research, Inc. (Mt. Prospect, IL). April 2002.

335. Institute for International Research Conference on Protein and Peptide Formulation Strategies for Drug Development and Delivery (San Francisco, CA). August 2002.

336. R&D Management Council Meeting of the Technical Association of the Pulp and Paper Industry (Cambridge, MA). November 2002.

337. DuPont Central R&D Center (Wilmington, DE). December 2002.

338. *ACTIVE*Pack 2003 Conference (Ponte Verde Beach, FL). February 2003.

339. International Symposium on Industrial Applications of Biocatalysis: *Chemical Development Issues* (Boston, MA). September 2003.

340. U.S. Army Workshop on Self-Decontaminating Materials and Multifunctional Coatings (Arlington, VA). October 2003.

341. British Royal Society Meeting on Biocatalysis in Alternative Media (London, England). December 2003.

342. National Autonomous University of Mexico (Mexico City, Mexico). March 2004.

343. Healthcare Research Initiative Workshop on the Effect of Radiofrequency Radiation on Pharmaceutical Product Quality (Cambridge, MA). June 2004.

344. Rensselaer Biotechnology Symposium on Biological Discoveries That Will Change the World (Troy, NY). September 2004.

345. Barnett International Conference: *The Consequences of Aggregation in Drug Development, Immunology, Quality Control, and Disease Genesis* (Philadelphia, PA). September 2004.

346. 4th Annual IBC Conference on Formulation Strategies for Protein Therapeutics (Boston, MA). October 2004.

347. U.S. Army Edgewood Chemical Biological Center (Aberdeen Proving Ground, MD). August 2005.

348. World Congress on Synthetic Receptors (Salzburg, Austria). September 2005.

349. International Conference “Celebrating 30 Years of Robert Langer’s Science” (Cambridge, MA). July 2006.

350. University of Montreal (Montréal, Québec, Canada). October 2006.

351. The Boeing Company Research Center (Everett, WA). December 2006.

352. Instrumentation Laboratory (Lexington, MA). December 2006.

353. Acambis Inc. (Cambridge, MA). January 2007.

354. 6th International Symposium on Industrial Microbiology and Biotechnology (Cambridge, MA). August 2007.

355. Scientific Conference on Chemical & Biological Defense Research (Timonium, MD). November 2007.

356. MIT Research and Development Conference (Cambridge, MA). November 2007.

357. Nanotech '2008 International Conference (Boston, MA). June 2008.

358. Materials Research Society Symposium (Boston, MA). December 2008.

359. Johnson & Johnson Research Briefing at MIT (Cambridge, MA). January 2009.

360. 3rd Annual Lyophilization Conference: *Ensuring Optimum Formulations for Pharmaceuticals and Biologics* (Boston, MA). February 2010.

361. DSM Corporate Research Center (Geleen, The Netherlands). June 2010.

362. Merck Serono Pharmaceutical Co. (Darmstadt, Germany). June 2010.

363. NanoFormulations '2010 International Conference (Stockholm, Sweden). June 2010.

364. Covidien Surgical Devices and Vascular Therapies Divisions (Cambridge, MA). October 2010.

365. World Lyophilization Summit (Cambridge, MA). May 2011.

366. Alvogen (Cambridge, MA). March 2012.

367. Colgate-Palmolive Co. (Cambridge, MA). April 2012.

368. FDA Parenteral Drug Association Glass Quality Conference (Washington, DC). June 2012.

369. University of Puerto Rico (Humacao, Puerto Rico). January 2013.

370. International Conference on Creating and Leveraging Intellectual Property in Developing Countries (Durban, South Africa – *via teleconference*). November 2013.

371. Northwestern University (Evanston, IL). April 2015.

APPENDIX B

Appendix B

Materials Reviewed by Professor Alexander M. Klibanov, Ph.D.

1. Joint Claim Chart with proposed constructions and intrinsic evidence identified by the parties
2. Patent and prosecution history for U.S. 7,612,102
3. Patent and prosecution history for U.S. 7,659,290
4. Patent and prosecution history for U.S. 7,659,291
5. Patent and prosecution history for U.S. 8,455,524
6. Provisional patent application 60/793,074
7. K. Connors, et al., *Chemical Stability of Pharmaceuticals* Chapter 7 (2d ed. 1986)
8. David W. Bates *et al., Consensus Development Conference Statement on the Safety of Intravenous Drug Delivery Systems: Balancing Safety and Cost*, 35 Hospital Pharmacy 151 (2000)
9. Portions of *Merriam Webster's Medical Desk Dictionary* (1996)
10. Cardene® I.V. Premixed Injection Ordering Information
11. *Guidance for Industry: Q1A(R2) Stability Testing of New Drug Substances and Products, Food and Drug Administration* (November 2003)